CHAPTER 15

Control of Airway Calibre and Assessment of Changes

Assessment of the responses of airway calibre to treatment or provocation is an important function of any pulmonary laboratory. This chapter reviews the procedures against a background of the control mechanisms.

15.1 Introduction

Static dimensions. The diameter (calibre) of the airways is normally appropriate for the size of the lungs. It is related to body size and is less in children than in adults. Relative to lung size the calibre can be greater in females than in males (Section 25.7). It varies with the depth of inspiration as this affects the radial traction on airways from the surrounding lung tissue. For the same reason, under quiet resting conditions the calibre is influenced by posture (Section 16.1.8).

Tone of airway smooth muscle. Airway smooth muscle is contractile and this property if unrestrained can lead to closure of small airways. Restraint is normally exerted by the rhythmic stretching that occurs during the inspiratory phase of the breathing cycle and reinforced by periodic deep inspirations. The inspirations appear to act by increasing airway circumference, stretching the smooth muscle cells and loosening the intracellular bridges that attach myosin to actin [1]. Under normal circumstances this mechanism ensures that smooth muscle tone is minimal and is reduced further during a deep inspiration. This is not the case in asthma when a deep inspiration can result in bronchoconstriction (Section 12.5.1). In most normal persons the absence of meaningful muscle tone has the important consequence that airway calibre is determined by static forces and is not increased by administration of bronchodilator drugs. However, the amplitude of tidal breathing is reduced during sleep or anaesthesia and the change contributes to diurnal variation in airway calibre (Section 32.4.3). Snoring or sleep apnoea can also result in hypoxaemia that itself increases bronchomotor tone.

A reflex increase in bronchial tone occurs in response to stimulation of receptors in the airways by inhaled foreign bodies, mucus and other materials. The resulting bronchoconstriction enhances the effectiveness of the cough reflex (Section 37.2.1).

Disease processes that affect the airways can reduce the extent to which inspiration stretches the airway smooth muscle. When this happens the airways are more susceptible to constriction in response to provocation. The airway calibre is then reduced (see Section 15.4), but can usually be at least partly restored by administration of bronchodilator drugs.

Other determinants of airway calibre are mediated by the autonomic nervous system, the endocrine system, reflexes arising within the respiratory tract and processes that regulate body temperature. Many of these control systems are subject to diurnal variation that contributes to the airway calibre being less at night

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than during the day. The bronchoconstriction can be augmented by hypoxaemia (see below, Reflex hypoxic bronchoconstriction).

In most generalised diseases of the lung the amelioration of airflow limitation is a principal objective of respiratory therapy.

15.2 Physiological control of airway calibre

15.2.1 Parasympathetic nervous system

Bronchoconstriction occurs mainly through activation of the parasympathetic nervous system by receptors in airways. These supply information to the nucleus ambiguus in the brain stem. From there cholinergic motor nerves, that form part of the vagus nerves, activate ganglia in the airway walls (Section 3.3.10). The postganglionic fibres act by release of acetylcholine and this stimulates muscarinic receptors (M receptors) on airway smooth muscle cells and related structures. Activation of the receptors causes the muscle cells to contract.

The parasympathetic innervation is mainly to the large airways where, in the absence of reflex activation it maintains some residual bronchomotor tone. The smaller airways are sparsely innervated so any narrowing of these airways is mainly from inflammation or loss of lung elastic recoil (see emphysema, Section 40.4). Narrowing may be partly controlled by the autonomic nervous system through acetylcholine activating goblet cells to secrete mucus. The action of acetylcholine is potentiated by anticholinesterases and inhibited by atropine and other substances, including ipratopium bromide, that compete with acetylcholine to occupy M receptor sites on the smooth muscle cells. In addition to acetylcholine, the airway muscle tone can be increased in other ways, including by substance P, a neurotransmitter for non-cholinergic excitatory nerves and by calcitonin gene-related peptide [2, 3]. The pharmacological control of bronchomotor tone has features in common with that of pulmonary vasomotor tone (Section 17.2).

Intrapulmonary reflexes. Bronchomotor tone is modulated by reflexes arising from receptors located throughout the respiratory tract and mediated via the vagus nerves. The tone is decreased by activation of stretch receptors as occurs during inspiration. It is increased by stimulation of receptors in the nasal mucosa that respond to cold, and by receptors in the larynx that respond both to many chemical substances and to mechanical stimulation. Bronchomotor tone is also increased by stimulation of nerve endings that lie beneath the epithelium of the airways. The receptors in the larger airways contribute to the cough reflex and can usually adapt quickly. The receptors in the smaller airways often adapt slowly. They can be stimulated by inhalation of a bronchoconstrictor aerosol (e.g. histamine) and by airborne irritants such as particles of respirable dust, tobacco smoke and sulphur dioxide (Sections 37.2.1, 37.3 and 37.4).

Reflex hypoxic bronchoconstriction. Hypoxia stimulates the carotid body (Section 23.5) to cause reflex bronchoconstriction that is mediated via the vagus nerves. This reflex is inhibited by isoprenaline. It can occur in patients with chronic lung disease and differs from other types of bronchoconstriction in responding to oxygen enrichment of the inspired gas [4]. The reflex can summate with other stimuli to bronchoconstriction, for example methacholine [5]. Hypoxia also causes pulmonary vasoconstriction (Section 17.2.2).

Other systemic reflexes. The aortic baroreceptors can initiate bronchoconstriction in response to a fall in the systemic blood pressure. Strenuous exercise can exert a bronchodilator effect that is partly due to diminution of vagal tone. The converse phenomenon of post-exercise bronchoconstriction can occur in asthma (Section 15.8.3).

15.2.2 Bronchodilator nerves

The only bronchodilator innervation to the airways is provided by non-adrenergic, non-cholinergic nerves. These nerves extend from the larynx to the terminal bronchioles and stimulation causes long lasting dilatation, especially of the larger airways. Stimulation can also activate mucous glands. The neurotransmitter substance appears to be vasoactive intestinal peptide (VIP) or the related substance, peptide histidine isoleucine. The role of this system in controlling normal airway tone is unclear [2, 3].

15.2.3 Sympathetic nerves

The sympathetic nervous system appears not to innervate the airway smooth muscles directly. Instead there are nerves to the mucous glands, the blood vessels and ganglia in the airway walls. The innervation to the ganglia provides a pathway whereby an increase in sympathetic activity can inhibit parasympathetic bronchoconstriction caused by the action of the vagi. It also causes bronchodilatation by releasing adrenaline to act on β_2 receptors in the airway walls. This action, unlike that of the vagus nerves, affects all classes of airway. A reduction in bronchial tone following administration of catecholamine drugs can be inhibited by β_2 blocking drugs such as propranolol and atenolol.

15.2.4 Effect of carbon dioxide

Deficiency of carbon dioxide in the intraluminal gas causes bronchoconstriction both reflexly and by a direct effect on bronchial smooth muscle. When the hypocapnia is generalised, as with hyperventilation, the narrowing affects all classes of airway. However, if the hypocapnia is localised, e.g. after a small pulmonary embolus, the bronchoconstriction is usually localised as well (see also pulmonary embolism, Section 17.2.3). The bronchoconstriction is reversed by the inhalation of CO_2 in a fractional concentration of 0.06. This concentration also partly reverses the bronchoconstrictor action of some drugs, for example histamine

and acetylcholine. Bronchoconstriction caused by hypocapnia is attenuated by atropine; this is evidence that the constrictor action is mediated in part via the vagus nerves [6]. The action is supplemented by a direct effect of CO_2 on bronchial smooth muscle. The mechanisms are under investigation [7]. These responses provide a mechanism whereby the ventilation to a part of the lung is adjusted in response to local variation in blood flow.

A material increase in the intraluminal concentration of carbon dioxide can cause paradoxical bronchoconstriction. This response is unaffected by atropine or isoprenaline and so appears to be a local reaction to a noxious stimulus, with the mechanism being unclear. It may arise in the bronchial muscle itself or be an axon reflex emanating from the larynx.

15.3 Atopy

Features. Some healthy persons respond to environmental allergens by producing increased quantities of immunoglobulin IgE. Such persons are said to be atopic. The condition has constitutional and environmental components [8] and puts an atopic individual at increased risk of IgE mediated diseases including infantile eczema, hay fever and some forms of asthma. The respiratory manifestations include an increased susceptibility to airflow limitation that gives rise to wheeze and breathlessness on exertion. These features may occur when exercising in cold air (Section 15.8.3), in response to provocation by inhalation of an aerosol containing histamine or methacholine (Section 15.8.2), or following exposure to occupational or environmental aerosols capable of causing asthma (Section 15.8.5, also 37.6.1 and 37.7.6). The same persons may also develop erythema and a weal on the skin following intradermal inoculation of a suspension of common allergens, such as house dust mite. The plasma concentration of immunoglobulin IgE is increased [9]. In many developed countries the prevalence of atopy has increased in recent years [10] but the incidence may now be levelling off. The reasons are unclear.

Assessment. Atopic status is usually assessed by skin testing using the anterior surface of the forearm. Drops containing antigen in suspension or solution are applied and each is then pricked into the skin with a clean needle. The needle is inserted obliquely to a depth just sufficient to lift the skin. A positive immediate reaction is the development of an itchy urticarial weal with diameter at 15 min usually in the range of 2–15 mm. Subsequently, after 10–40 min the weal temporarily becomes surrounded by erythema. A delayed reaction to a specific test antigen is likely to occur after 8–24 h, so if this is a possibility the site of innoculation should be reassessed at these times. Test antigens that might be used are: house dust mite, pollen of local grass and danders from dogs and cats to confirm atopic status, the suspected antigen (if there is one) and a saline control. In many circumstances a histamine (positive) control is used as well. To avoid an anaphylactic reaction developing in a highly sensitised subject, any non-standard antigen should be used initially in very low concentration along the lines described subsequently for inhalation challenge (Section 15.8.5).

15.4 Pathological causes of generalised airflow limitation

Increased tone in bronchial smooth muscle (bronchoconstriction). This abnormality causes narrowing that can affect any or all classes of airway. When present the change reduces the ventilatory capacity and gives rise to wheeze and breathlessness on exertion. Other features of airflow limitation are summarised in Section 14.3.5. The changes are reversible in response to treatment with broncho-active drugs.

Bronchoconstriction is an important feature of asthma (Section 40.2). It also occurs as a consequence of exposure to atmospheric or domestic air pollution (including tobacco smoke) or pollution of occupational origin. The effects of the different pollutants are cumulative and can cause severe limitation to airflow. However, much of the limitation can be due to associated structural changes arising from chronic inflammation in the airway walls. The latter condition is described as chronic obstructive pulmonary disease (COPD, see below and also Sections 37.3 and 40.3).

The increased bronchomotor tone is often due to stimulation of receptors that activate parasympathetic cholinergic nerves. This pathway responds to pharmacological interventions (Section 15.7.1). An additional stimulus to bronchoconstriction comes from substances that reach the environment of the muscle cells as part of a pathological response; the substances include some that emanate from the muscle cells themselves [11]. A role has also been suggested for inflammation in or around small airways interfering with the mechanism whereby respiratory movements lower the bronchomotor tone (see above Increased tone in airway smooth muscle). At the time of writing, the evidence is indirect [1, 12] and not fully worked out.

Structural changes in and around airways. Structural changes, described as *airway remodelling*, occur in response to inflammatory agents that are formed in the lung. The stimulus arises either from an allergic reaction, as in most cases of asthma, or is a result from release of mediators by neutrophils and other phagocytic cells as may occur in COPD (Section 40.3). Where the target is bronchial smooth muscle, this can generate further mediator substances. The inflammatory changes affect the small airways; they include vascular engorgement, interstitial oedema, infiltration of airway walls by inflammatory cells and extrusion of secretions and cell debris into the airways. These changes can occur in both asthma and COPD but the mechanisms, natural history and responses to treatment are different [13], see also Chapter 40. However, with passage of time the features of the airways in the two conditions may converge [14]. Differences in the lung parenchyma remain.

Asthma. The predominant inflammatory cells are eosinophils, lymphocytes and mast cells, the limitation to airflow is episodic and, except in the late stages can be expected to respond to therapy (Section 40.2).

COPD. The predominant inflammatory cells are neutrophils and macrophages. The airways obstruction is typically progressive and only partially responsive to bronchodilator therapy. As a result, acute episodes are usually superimposed on a progressive slow deterioration in function that often responds poorly to present standard treatment (Section 40.3). The condition can be preceded or accompanied by chronic bronchitis, but this is not invariable. In the longer term structural changes can occur in the lungs. Either fibrous tissue can be laid down that permanently constricts the affected airways or the lung parenchyma can be digested by proteolytic enzymes leading to weakening of its structural framework. This condition is emphysema (Section 40.4).

Combined abnormality. Some patients with airway narrowing that is mainly irreversible can have a significant reversible element to their airflow limitation, while in some asthmatics the flow limitation can become largely irreversible [14]. Patients who present at this stage in their illness can be described as having chronic non-specific lung disease (CNLD) or chronic airways obstruction (CAO).

15.5 Bronchodilatation as a diagnostic tool

From a clinical perspective a respiratory patient with variable airflow limitation that is reversed fully by bronchodilator and related therapy has asthma. One in whom the limitation is not fully reversible has COPD [15]. This classification includes amongst patients with COPD some in whom the reversible element is small and others in whom it is relatively large, verging on asthma. That the latter patients might actually have asthma has led some authorities to redraw the boundary between the two conditions. A reversibility that exceeds an arbitrary percentage of the reference or baseline value then becomes asthma whilst a lesser change is COPD. Changes in forced expiratory volume of 9%, 10% and 12% have been used for this purpose. The dichotomy assumes that the test expirations have been maximally forced since with submaximal effort the volume of gas expired in one second (relaxed expiratory volume) can be increased [Section 12.4.1]. In addition, patients vary in their susceptibility to individual bronchodilator drugs and to combinations of drugs, when the order of administration can influence the outcome. Thus, bronchodilator status should preferably be based on the optimal response not that to a single drug. However, for patients classified as apparently having COPD, the optimal bronchodilator response can cross and re-cross the diagnostic boundary during the course of the illness. The response appears to be normally distributed and does not reflect the lung pathology. Thus, an arbitrary responder status does not provide a sound basis for diagnosis where this is in doubt, nor for decisions on treatment [16, 17].

15.6 Physiological features of airflow limitation

Generalised narrowing of large airways (diameter >3 mm) is mainly due to an increase in bronchomotor tone, whilst narrowing of small airways is mainly a consequence of inflammation with or without a reduction in elastic recoil. The changes can sometimes be visualised by tomography (HRCT). They can be inferred from the results of physiological tests (Table 15.1).

Some consequences of bronchial provocation leading to narrowing of mainly the larger airways is shown in Fig. 15.1. The converse situation of bronchodilatation improving indices of forced expiratory flow is shown in Fig. 15.2 and Table 15.2.

Table 15.1 Some indices that reflect narrowing of lung airways.

Aspect	Mainly large airways	Mainly small airways
Ventilatory capacity	FEV_1, FVC, MVV, PEF & Tiffeneau Index reduced. (FEV% can be unchanged) Wheeze*	$FEF_{75\% \text{ of initial FVC}}$ (flow at iso-volume) reduced Dispersion of transit times increased
Lung mechanics	Specific conductance (sGaw) reduced Dynamic compliance (Cdyn) reduced Other, including impedance*	
Lung volumes	Residual volume increased. V_A'/V_A reduced. Closing volume increased	
Gas distribution	Desaturation*	Lung mixing, including single breath N_2 index, aerosol bolus dispersion & N_2 slope increased
Gas exchange	Transfer factor unchanged (but reduced if calculated using V_A', Section 20.9.1)	R index of $\dot{V}_A / \dot{Q}$ inequality impaired Exercise ventilation increased (Section 28.4.7)

* particularly in children e.g. [18, 19]

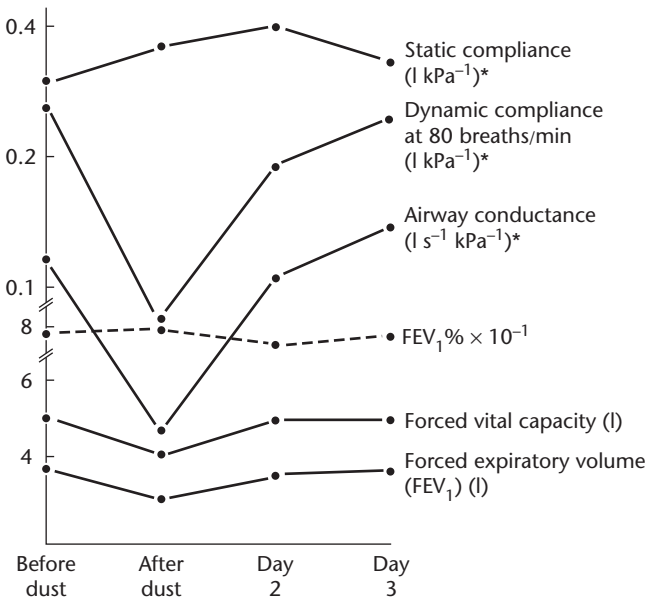

Fig. 15.1 Effect of mild bronchial obstruction caused by inhalation of cotton dust upon the lung function of a healthy subject. The semi-log scale indicates the relative magnitudes of the changes. In this instance, airway conductance and dynamic compliance were highly informative whereas FEV% and static compliance were not. *To convert to traditional units (L and cmH_2O) multiply by 10.
Source: McDermott M, personal communication.

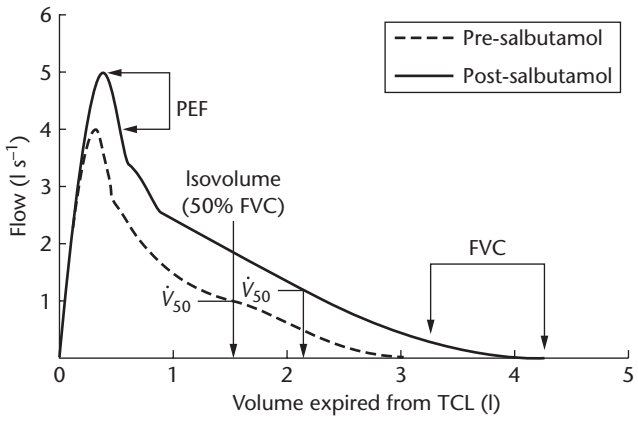

Fig. 15.2 Flow–volume curves before and after inhalation of a bronchodilator aerosol in a patient with airflow limitation that was partly reversible. The numerical results are given and interpreted in Table 15.2.

15.6.1 Calibre of larger airways

The above examples demonstrate that any of a number of lung function indices can be used to monitor variations in calibre of larger airways, including whole body plethysmography, dynamic spirometry and forced oscillometry.

Airway conductance. When the medical condition involves narrowing of large airways the best indicator of bronchodilatation is an increase in airway conductance (*G*aw) (Fig. 15.1). The measurement is made during tidal breathing so is not modified by reflex bronchodilatation from a prior full inspiration, as is an integral feature of most other tests. The conductance should be expressed at constant lung volume and not as specific conductance (s*G*aw = *G*aw/thoracic gas volume), since s*G*aw is not completely independent of lung volume (Section 14.3.4). Dynamic compliance can also be used (Fig. 15.1). The measurement of conductance (Section 14.3.4) is available at specialist centres where it is sometimes used for monitoring bronchial hyper-reactivity.

Single breath indices, FEV_1. This index is affected by narrowing of both large and small airways and is the index of choice in most circumstances. It is not suitable for young children or others who cannot cooperate in the measurement; for such subjects the impedance or other methods should be used instead (Table 15.1). FEV_1 has the disadvantage for some applications that the procedure may itself influence airway calibre, particularly in asthma, where both the initial inspiration to TLC and expiration to RV can increase bronchomotor tone [20]. Where these effects may be important, the conductance or indices from

Index	Before	After	% change*	Reference value
FEV_1 (l)	1.64	2.20	29	3.10
FVC (l)	3.24	4.34	29	4.43
$FEV_{1\%}$	50.6	50.7	0	66.1
IVC (l)	3.70	4.32	15	4.43
Tiffeneau index	44.3	50.9	16	66.1
PEF (l s^{-1})	4.1	5.1	22	8.9
$FEF_{50\%\ FVC}$ (l s^{-1})	1.0	1.2 †	18	3.0
TLC (l)	7.98	7.99	0	7.44
RV (l)	4.28	3.67	–15	2.68
TI (mmol min^{-1} kPa^{-1})	9.81	9.84	0	9.5

* expressed as $100 \times \Delta x/\bar{x}$
† flow at isovolume = 1.9 l s^{-1}; change in flow at isovolume = 62%.

Table 15.2 Improvement in single breath indices of lung function following bronchodilatation in the patient with airflow limitation whose maximal expiratory flow volume curves are given in Fig. 15.2 (male, age 69 yr, height 1.84m, body mass 60 kg). The response was detected by FEV_1, PEF and flow at isovolume, but not by $FEF_{50\%\ FVC}$. Tiffeneau index (FEV_1/IVC) was informative whereas FEV% (FEV_1/FVC) was not.

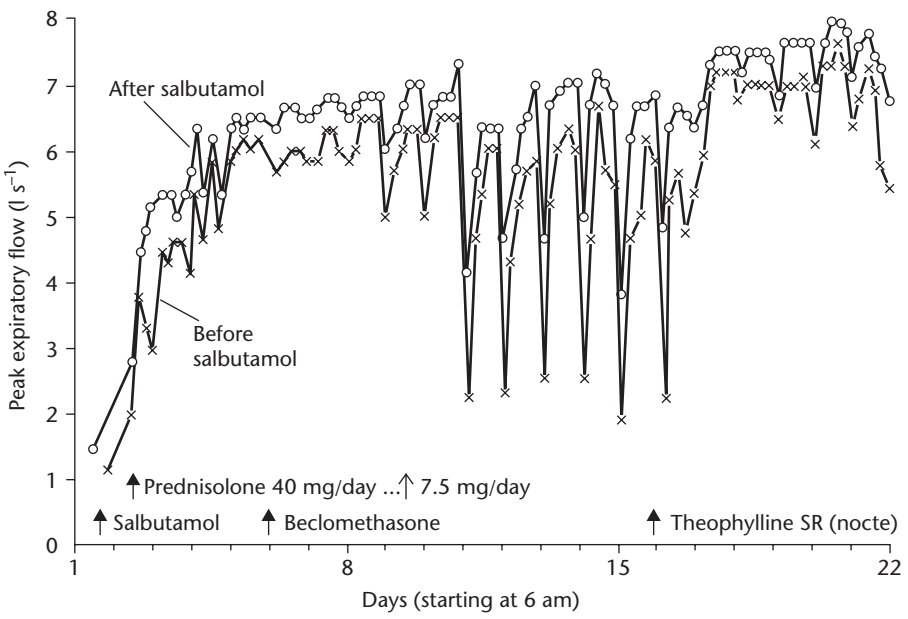

Fig. 15.3 Peak flow chart showing stages in the establishment of a suitable bronchodilator regimen in a patient with severe airflow limitation. Salbutamol by inhalation only had a small effect (indicated by the vertical distance between the two lines). The condition responded to oral prednisolone in high dosage. Changing to maintenance dose plus inhaled beclomethasone resulted in loss of control, which was reestablished when an evening dose of slow release theophylline was added to the regimen. The use of a long acting sympathomimetic drug might have achieved a similar result.
Source: [21].

a partial expiratory flow–volume curve should be used instead (Section 12.5.1).

Peak expiratory flow. PEF is appropriate for serial measurements (Figs 15.3 and 15.7) and for home monitoring. However, peak flow can mislead if the calibration is alinear or the technique is incorrect (Section 12.3.2). The result can also mislead if the expiratory muscles are weak or if the compliance (flaccidity) of the walls of large airways is increased by the drug that is being assessed. The index does not detect narrowing of small airways.

Indices that relate to vital capacity. Some indices in this category, including FEV_1/FVC (FEV%) and forced mid-expiratory flow (FMF, also designated $FEF_{25-75\%FVC}$, Section 12.4.1), are invaluable for detecting the presence of airway obstruction but misleading for detecting changes. This is because an increase in airway calibre not only increases ventilatory capacity, but also reduces airway closure during expiration, so vital capacity is often increased as well (Fig. 15.2). As well as the above indices, similar considerations apply to forced expiratory flows when 50% or 25% of vital capacity remain to be expired. FEV% can paradoxically fall if the bronchodilator effect increases FVC more than the FEV_1 (Fig. 15.1). Indices based on flow (other than peak flow) should only be used when they can be measured at the same thoracic gas volume before and after administration of the bronchodilator drug [22]. The volume should then be measured by whole body plethysmography. This procedure is mainly of research interest.

15.6.2 Calibre of small airways

In some patients the main site of airflow limitation is the small airways. In this circumstance a change can usually be monitored using FEV_1, but not PEF or an index of airways resistance. However, some patients report an improved quality of life, reduced breathlessness on exertion or an increase in exercise capacity despite there being little change in FEV_1 [23–25]. In this circumstance the improvement appears to reside in small airways.

15.7 Bronchodilator therapy

15.7.1 Pharmacological and clinical aspects

Bronchodilator therapy is usually the most important component of treatment for airflow limitation. The treatment is likely to also include measures directed against both the cause of the limitation and the underlying medical condition, especially any accompanying inflammation in small airways. The latter can respond to anti-inflammatory drugs, usually a corticosteroid drug, so the two forms of therapy should be considered together.

The bronchodilators in current clinical use are short and long acting β-adrenoceptor agonists, anticholinergics and methylxanthines [26]. In acute childhood asthma intravenous magnesium sulphate can provide additional benefit. Agents that may sometimes prevent, but do not alleviate airflow limitation, such as sodium cromoglycate and leukotriene antagonists can be used as supplements.

β-adrenoceptor agonists. These drugs are derivatives of noradrenaline that binds to β_2 receptors on smooth muscle cells and some other structures. The principal action is to inhibit or reverse bronchoconstriction from any cause, of which the most common (in the absence of local inflammation) is increased parasympathetic activity mediated by acetylcholine. The mechanism entails increased intracellular production of cyclic AMP

and other changes that affect calcium-activated potassium channels on the cell membranes (maxi-K channels).

The β_2-agonists are administered preferably by inhalation, from a nebuliser, but can be taken orally. They have a good safety record unlike less selective drugs that can cause tachycardia and/or aggravate hypoxaemia [27]. A possible difficulty is that the bronchodilator response can become attenuated through the development of tolerance, but the change is seldom of sufficient magnitude to affect clinical management.

Anticholinergic drugs. These drugs compete with acetylcholine to occupy muscarinic receptors on smooth muscle cells. The process is dose dependent until all receptor sites are occupied. However, the receptors are of more than one type so there is a prospect of more selective blocking agents being developed. The mode of action is indicated under Parasympathetic nervous system above (Section 15.2.1). The drugs are administered by inhalation or nebulisation and side effects appear not to be a problem. Their action complements that of the β_2-adrenergic drugs and their effectiveness as bronchodilators is similar [28]. However, β_2-agonists are rather more effective in asthma, possibly because some bronchoconstriction is caused by leukotrienes or other inflammatory mediator, so is not of parasympathetic origin. Conversely, the anticholinergics may be better for COPD since both more of the bronchoconstriction is of reflex origin than in asthma and the action of the drug in suppressing the activity of goblet cells may be beneficial.

Methylxanthines. Over many years theophylline by mouth or intravenously has been found to be effective for relief of airflow limitation in some patients (e.g. Fig. 15.3). However, the mechanism is uncertain. The drug acts when given orally or intravenously, not by inhalation and its effectiveness is related to the plasma concentration. The action is on mast cells, suppressor T-lymphocytes (CD8+) and as an adenosine antagonist. Theophylline may also increase the contractility of fatigued diaphragm, but the evidence is inconclusive. It appears to act as an anti-inflammatory agent to increase the patency of small airways. Possibly on this account theophylline is widely used to increase the exercise capacity of some patients with COPD; the improvement occurs despite little change in ventilatory capacity [24].

Overview of treatment of airflow limitation. In most instances the immediate cause for acute limitation of airflow is an increase in the tone of bronchial smooth muscle. This is effected by the local parasympathetic nerves in response to stimulation by acetyl choline. It is reversed by inhalation of an aerosol containing an antidote; the most effective choice is usually a substance that activates sympathetic receptors in the airways (β_2 agonist), but an atropine analogue that blocks the muscarinic receptors for acetyl choline (e.g. ipratropium bromide) can also be used. The two classes of drug have different response times and can be used in combination. When the flow limitation is due to asthma the underlying inflammation in small airways is controlled with an anti-inflammatory corticosteroid drug. For recurring flow limitation the short acting bronchodilators can be replaced by longer acting analogues (e.g the β_2 agonists salmeterol or formoterol and the atropine analogue tiotropium). When the underlying cause is asthma a long-acting β_2 agonist can be combined with a corticosteroid drug in one preparation [29]. An anti-leukotriene drug may be of some help. In COPD a long acting atropine analogue can be the medication of first choice [30]. Inhaled corticosteroids, which reduce the frequency of exacerbations, can be tried under close observation, as can other classes of drugs including theophylline (Fig. 15.3, also [31]).

Disease severity as basis for treatment. The majority of patients with potentially reversible airflow limitation respond to one or more of the remedies that are listed in the previous paragraph. The treatments can be prescribed progressively, or the starting point can be selected in the light of clinical experience or from guidelines based on the initial limitation to airflow. The latter is usually graded in terms of forced expiratory volume (FEV_1), FEV/FVC or peak expiratory flow (PEF) [32]. However, use of PEF has disadvantages (Section 12.3.1), so in most circumstances, including in general practice, FEV_1 and FEV% should be used [14, 33]. The level can be the basis for treatment. This has the advantage of being unambiguous, but the guideline may lead to the initial treatment being sub-optimal if the patient's circumstances do not match those on which the algorithm was based. Where the algorithm has claims for universality further difficulties can arise [34, 35].

Administering a drug by inhalation. The objective is to deliver an effective dose to the bronchial epithelium with minimal deposition in the mouth, pharynx or lung parenchyma. This is best done using a monodispersed aerosol (Section 37.2.4), but appropriate dispensers are not widely available. Most patients use metered dose inhalers (MDI) which discharge into the mouth or into a spacer from which the aerosol is inhaled. The spacer, which can come in any of several sizes is a hollow vessel that is in series between the inhaler and the mouth. Its use reduces the need for accurate timing of the discharge from the inhaler and eliminates by sedimentation any large droplets of aerosol that might otherwise give rise to symptoms. Other aerosol dispensers are also used or the material can be delivered as a powder. In all instances the usage should be in accordance with the manufacturer's instructions (e.g. Table 15.3). Alternatively, the material can be inhaled during regular breathing from a nebuliser that is driven by a supply of compressed gas. This should preferably be air. When oxygen is used a watch should be kept for hypoventilation (Section 35.7.2). Nebulisers are popular with patients but expensive and give large doses. An MDI with spacer can deliver an equivalent dose of bronchodilator. Except for acute treatment, a nebuliser should only be used after an assessment based on objective criteria has been carried out.

Many patients coming for assessment will already have inhalers and approximately 30% are likely to use them incorrectly. Hence,

Table 15.3 Some practical aspects of aerosol administration.

To start. Shake dispenser	
Exhale to residual volume	
For MDI. Insert nozzle into open mouth.	*For spacer*. Grip outlet with lips.
Actuate mechanism and concurrently make full inhalation at moderate rate	Actuate mechanism, then make full inhalation at moderate rate
Close mouth. Hold breath for at least 5 s	
Repeat once after 1 min	

the assessment provides an opportunity to check the patient's technique and to provide retraining. A placebo inhalant can be used during training.

15.7.2 Measurement aspects

What constitutes a bronchodilator response? A decrease in airway calibre can be noticed as tightness of the chest, wheeze or increased breathlessness on exertion. The awareness is greatest if the change occurs rapidly and if the subject's sensory perception is above average. Under controlled conditions an improvement in FEV_1 of as little as 4% can be detected [36], so this increase or the equivalent reduction in symptoms or increase in exercise capacity [37] sets a lower limit to what might be considered a worthwhile improvement. Another limit is that the change should exceed the normal measurement error, which in the case of FEV_1 is of the order of 0.16 or 0.18 l [38, 39]. This is a trivial change for someone with a normal FEV_1 but in percentage terms can be a very large change for someone with a very low FEV_1. However, changes in symptoms are not experienced in absolute units but as proportional deviations from an existing level (Weber–Fechner law [40]), so the target change above a predetermined minimum is best expressed as a percentage. This might be an increase in FEV_1 of 12% of predicted value, as can be used for diagnosis of asthma, or 15%. Where there is little change in FEV_1 the criterion can be a comparable improvement in exercise capacity or other feature identifiable using a quality of life questionnaire (Section 8.2.6). A patient is unlikely to persist with a symptomatic treatment that he or she feels to be ineffective.

An intention to report an improvement as a percentage change raises the question as to how it should be expressed. For two determinations of FEV_1 before and after bronchodilator (x_1 and x_2, respectively), the usual format would be:

$$100(x_2 - x_1)/x_1 \qquad (15.1)$$

but this model in which the reference is to the initial level, has a poor reproducibility [41, 42]. The scatter is due to regression to the mean and can be avoided by relating the change due to the treatment not to the initial but to the mean level (see Section 5.4.2), hence:

$$100(x_2 - x_1)/0.5(x_2 + x_1) \qquad (15.2)$$

Unfortunately, this model is seldom used. Alternative denominators that have been suggested are the reference value for FEV_1 and either the maximal possible improvement in FEV_1 ($x_{pred} - x_1$) or the maximal attainable improvement ($x_{2,\max obs} - x_1$) [40, 41]. Results expressed in this form are an improvement on eqn 15.1, but do not meet the requirement of proportionality encapsulated in the Weber–Fechner law.

In addition, all these models describe the response in terms of a peak effect (possibly qualified by time from administration) but neglect the duration. The latter can be incorporated in the result by making serial measurements, then constructing a response–time curve and measuring the area under the curve. Alternatively, the curve should be represented mathematically and the overall result described by the parameters (coefficients) of the resulting equation [43]. This appears not to have been achieved in practice.

Assessment of individual patients

A routine assessment in a patient is usually performed by making measurements of FEV_1 before and after inhalation of an appropriate aerosol; this is usually a short acting β_2 adrenergic or anticholinergic drug (Section 15.7.1). The subject should not have used his or her inhaler and preferably not smoked a cigarette during the 4 h before the test. Where the assessment is for any evidence of reversibility of airflow limitation, the period of abstinence should reflect the time to nearly full response of all the drugs that the patient is receiving (e.g. 15–30 min or 9 h). Excitement or strenuous exercise are best avoided. The result is greatly influenced by the quality of the measurements, so these should be made in an unhurried manner by a recommended method.

Establishing a baseline. A positive result to a single test of bronchodilatation is usually an indication to start treatment, but this need not be so [44] and a negative response does not exclude this possibility. Greater certainty is achieved by first making base-line measurements over a few days then assessing the response to the drug at more than one time of day. When this is done the time between treatments should be at least 4 h.

Serial measurements. Serial measurements (e.g. Fig. 15.3) are essential when the bronchial tone is labile or the response is not immediate or uncertain, when the drug can cause euphoria and when the administration is prophylactic. For example, to

assess the benefit from steroid drugs the assessment might be performed twice daily for three periods of 7 to 14 days with the drug administered during the second period only. In the case of prednisolone the dose might be 0.6 mg/kg daily for at least 14 days [45]. An assessment of at least over two weeks is required to test the effect of inhaled corticosteroids and can also then test whether the drug has helped to prevent bronchoconstriction in response to provocation with a specific antigen (Section 15.8.5).

Assessment involving groups of subjects

For a clinical trial that compares two drugs on a group of subjects the study design should be overseen by a statistician [46, 47]. The protocol should specify the class of patient, the state of health and the smoking status at the time of study. The airway calibre and amount of resting bronchomotor tone should be similar at the start of each period of treatment. The response should include the magnitude and the duration of bronchodilatation. This can be done by adjusting the doses so that both drugs produce the same initial response, then recording the subsequent amplitude and duration by serial measurements [48]. The measurements should be continued until the response has returned to its control level. Interpretation of the result should take account of circadian variation (Section 25.6). Where the trial is of a clinical nature, criteria involving symptoms and exercise tolerance should be included in addition to spirometry [49].

15.8 Bronchial hyper-responsiveness

15.8.1 Underlying considerations

Definitions. Airway *hyper-responsiveness* indicates that there is an increased tendency of the bronchi to constrict in response to stimulation. The term is a general one and has two notable components. The *sensitivity* of the airways indicates the threshold concentration of histamine or other substance that is required to initiate bronchoconstriction. In hyper-responsive subjects the threshold is diminished. The *reactivity* of the airways describes the change in airway calibre effected by a given increase in strength of the provoking stimulus (dose–response relationship). These features are apparent to variable extents in charts illustrating the response to inhalation challenge (Fig. 15.4 and Fig. 15.5). The *maximal response* is the plateau value seen in the dose–response relationship of most persons with healthy lungs. A plateau is uncommon in atopic individuals and seldom occurs in persons with asthma (see Fig. 15.5, also Tone of airway smooth muscle, Section 15.1). Where a plateau is achieved it is greater for histamine than for methacholine and if obtained with histamine is not affected by the additional presence of methacholine [51].

Biological variability. People differ in the responsiveness of their bronchial smooth muscle to agents that cause bronchoconstriction. The most important factor is atopic status; this dimension of a person's constitution and the method by which it is usually assessed are given in Section 15.3. Some 20% of most western

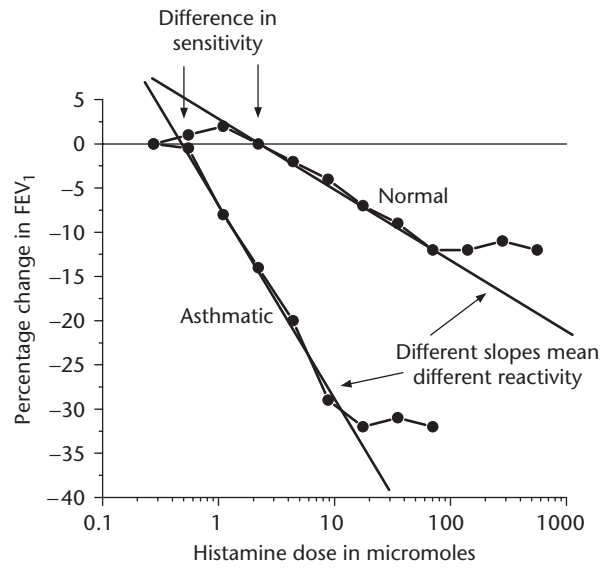

Fig. 15.4 Change in FEV_1 with increasing dose of histamine in two individuals. In the normal subject the FEV_1 did not start to fall until a dose of 4 μmol whereas in the patient with mild asthma the fall began at 1 μmol (a difference of sensitivity). The rate of drop in FEV_1 per unit dose was steeper in the asthmatic and so the asthmatic was more reactive.

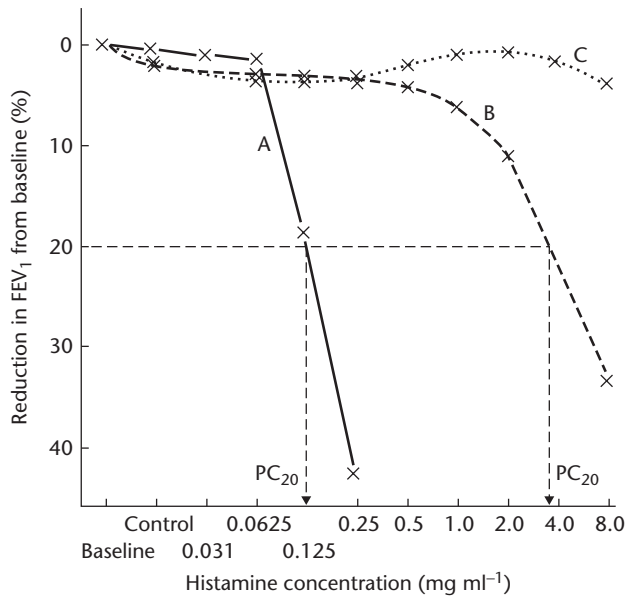

Fig. 15.5 Testing for bronchial hyper-reactivity in subjects suspected of having asthma. The FEV_1 was normal between attacks. The subjects inhaled saline and then graded doses of histamine solution from a Wright nebuliser for 2 min with 3 min intervals in between. Measurements of forced expiratory volume were made every 0.5 min. Subject A showed marked hyper-reactivity; subject B was moderately reactive; subject C did not react to histamine in the dosage used. The small reduction in FEV_1 occurring after the control inhalation of saline was probably physiological. Had the reduction been bigger the test would have had to be postponed as the challenge result could not have been interpreted satisfactorily. Source: [50].

Table 15.4 Aspects of respiratory sensitisation.

Aspect	Procedure for assessment (including outcome)	Comment
Atopy	Skin prick test weal diam >2mm Serum IgE >350 μg/ml	Responders at increased risk of sensitisation to some occupational allergens
Bronchial hyper-responsiveness	Non-specific bronchial challenge (histamine, methacholine, exercise, cold air)	Often accompanies occupational asthma
Temporal variation in PEF	Morning dip pattern (Fig. 15.6). Decline over working day or working week (Figs 15.7 and 8)	Measurements should extend over weekends and holidays
Asthma or alveolitis	Inhalation challenge test (Fig. 15.8) Radio allergosorbent (RAS) test	Can be confirmatory Carries small risk of sensitisation Identifies specific IgE in serum

populations are atopic [10]. Such persons have an increased sensitivity to some stimuli, e.g. to cold air (Sections 36.2 and 36.3). They readily become sensitised to antigenic dusts that cause extrinsic asthma, including occupational asthma (Section 37.7.6). Other than atopy, the susceptibility to bronchoconstriction is influenced by previous exposures to irritant or antigenic particles, inflammatory changes in the airways (such as occur with extrinsic allergic alveolitis), pulmonary congestion and possibly other factors. An increased response can be specific to one substance (e.g. an agent that causes occupational asthma), it can reflect interaction between stimuli (e.g. an allergen and oxides of nitrogen, Section 37.4.4) or be non-specific such that any constrictor stimulus can elicit an exaggerated response. Non-specific bronchial hyper-responsiveness also occurs in approximately 5% of persons who in other respects appear to have completely healthy lungs. Hyper-responders can be said to have 'twitchy' airways. Some aspects of respiratory sensitisation are indicated in Table 15.4.

The presence of sensitisation to a single substance is assessed by specific *bronchial challenge*. This entails the subject inhaling the relevant aerosol under controlled conditions. In other circumstances the assessment is of bronchial hyper-responsiveness to inhaled methacholine, histamine or other provoking agent. The extent of spontaneous variability in peak expiratory flow is not an adequate substitute [52].

15.8.2 Non-specific bronchial challenge

Indications. Non-specific bronchial challenge can be used as a screening test in epidemiology or occupational medicine. It can be a diagnostic tool for assessment of a patient whose medical features are consistent with asthma but in whom the response to bronchodilator therapy appears not to be compatible with that diagnosis. In this circumstance a negative response argues against asthma. A positive response can be confirmatory, but only when it is pronounced. The test is also used to confirm the effectiveness of prophylactic treatment with inhaled corticosteroids or other drug.

Contra-indications, precaution and side effects. A non-specific challenge test is normally considered safe when carried out according to a recommended protocol, provided the subject is not pregnant and does not have moderately severe asthma or another condition that might affect the outcome. (Table 15.5).

The procedure is considered to be safe when carried out according to the recommendations; these include the deployment

Table 15.5 Medical contra-indications to non-specific bronchial challenge testing.

Condition	Contra-indication: Absolute	Contra-indication: Relative
Asthma	FEV_1 < 50% predicted or < 1 l or 1.2 l*	FEV_1 <60% predicted or <1.5 l in men, 1.2 l in women
Other	Myocardial infarction or stroke in last 3 months Aortic aneurysm BP > 200/100 mm Hg Pregnancy	Nursing mother On cholinesterase inhibitor, e.g. for myasthenia gravis Epilepsy requiring treatment Upper respiratory tract infection in last 2 weeks

* Respectively from ATS and ERS guidelines. Sources: [53, 54, 55].

of trained personnel, and having medication for bronchospasm and equipment for resuscitation immediately available. After the test up to 25% of subjects may experience some chest tightness, cough or other symptom. The symptoms are usually mild and of short duration. They are probably less frequent after methacholine than after histamine. However, histamine is possibly safer as the induced bronchoconstriction appears to be more easily reversed by salbutamol. Staff may also be affected [56] and in order to protect them and prevent premature bronchoconstriction in patients the room should have good ventilation and contamination of the air should be minimised by use of a low resistance filter on the exhalation port from the equipment [53]. Reactive persons should not administer the test.

The results are influenced by the prevailing level of bronchomotor tone, the drug and the method of delivery that are used, the method of detecting bronchoconstriction and the index that is employed. These features should be standardised and taken into account when interpreting the findings [57]. Most laboratories follow the recommendation of ATS in administering methacholine and monitoring the response by spirometry [53].

Practical details. Monitoring the response is usually in terms of FEV_1. However, the index has the disadvantage that the full inspiration can elicit bronchodilatation (see below Problems with the measurement). Thus, for maximal accuracy airway conductance (s*G*aw) or total thoracic resistance (*R*tot) [19] should be used instead. The last of these procedures is suitable for young children.

The reasons for performing the test, the condition of the subject, the safety precautions and related matters should conform to the conventions listed above. The subject should not currently be in receipt of bronchodilator therapy or be recovering from or have a viral infection. The initial FEV_1 should normally be greater than 70% of the reference value [54]. Smoking and drinks containing caffeine are best avoided during the 4 h prior to the test. Test solutions in appropriate concentrations made up in 0.9% saline (Table 15.6) should be at hand. They should be administered by inhalation, either for 2 min from a Wright nebuliser (5 ml of solution nebulised at a flow 8 l min^{-1}), five vital capacity breaths from a demand nebuliser (e.g. De Vilbiss) or five tidal breaths from a dosimeter. The drug delivery system should preferably have been calibrated in order that the results can be comparable between laboratories [57]. Further details and examples of the outcomes are shown in Figs 15.4 and 15.5.

To undertake the test a base line measurement is made in duplicate using the chosen index (usually FEV_1). The *lowest* of the chosen concentrations of methacholine (or histamine) is then administered as the *first* provoking dose. After 30 s and again after 90 s from the completion of the inhalation the physiological measurement is repeated; usually a single determination is sufficient but depending on its quality up to two repeats are permissible; in the case of FEV_1 the higher should be reported [53]. The next lowest concentration of aerosol is then administered and this sequence is repeated until an endpoint is reached. The intervals between inhalations should not exceed 5 min. At the end of the test any airflow limitation is reversed with salbutamol or other β_2 stimulant drug.

Table 15.6 Methacholine dosing schedule for 2-min tidal breathing method. Using the full procedure the first challenge is at level J (see also Short procedures below).

Designation	Dose (mg ml^{-1})*	Dilution
A	16	100 mg MetaCholine Chloride +6.25 ml 0.9% saline
B	8	50% of above
C	4	50% of above
D	2	50% of above
E	1.0	50% of above
F	0.5	50% of above
G	0.25	50% of above
H	0.125	50% of above
I	0.0625	50% of above
J	0.031	50% of above

* Interpretation of PC_{20}(expressed as dose of methacholine, mg ml^{-1}):
>16 normal bronchial reactivity;
4–16 borderline hyper-reactivity;
1–4 mild hyperactivity (positive test);
<1 moderate to severe hyperactivity.
Source: [53].

The endpoint is when a 20% reduction in baseline FEV_1 or 35% reduction in sGaw has been achieved, or the maximal agreed concentration of aerosol has been administered. The endpoints are obtained by interpolation of a semi-log plot of FEV_1 or s*G*aw on aerosol concentration or dose (Fig. 15.5). The result is in terms of either the last provoking concentration to be administered (PC_{20}, FEV_1 or PC_{35},s*G*aw), or the cumulative dose up to this point (PD_{20},FEV_1 or PD_{35},s*G*aw). If one subject is to be tested the procedure takes up to 1 h.

Short procedures and adaptations for respiratory surveys. The procedure can be shortened by using a lower end point (e.g. a 10% reduction in FEV_1), by leaving out alternate test concentrations or by omitting the lower test doses. The first two measures considerably reduce the sensitivity of the test, whilst the third can be hazardous in reactive subjects. In respiratory surveys, where a subject's answers to questions indicate they are unlikely to react, a higher starting dose can be administered. The procedure can also be shortened by monitoring the specific conductance instead of the forced expiratory volume.

Where a subject's FEV_1 fails to drop by 20% the test does not provide a quantitative score suitable for statistical analysis. This difficulty can be overcome by deriving an index of response using the slope of the relationship of the percentage reduction of FEV_1 on the final cumulative dose of the drug. This is called the log

dose slope [59] and is calculated from

$$\text{LDSFEV}_1 = \log_{10}((\%\text{ change in FEV}_1)/(\text{total cumulative dose}) + 1) \quad (15.3)$$

Its use is recommended for population studies where estimates of bronchial hyper-responsiveness are required [60].

Interpretation. When the response is to methacholine, a PC_{20} FEV_1 of 16 mg ml^{-1} is normal and excludes a diagnosis of asthma, whilst a PC_{20} of 1 mg ml^{-1} or less on first assessment can be taken as evidence for the condition. However, with methacholine the effect can be cumulative, so a second test within 24 h of the first can yield a false positive result. Interpretations of intermediate results are given in Table 15.6. A false positive result can also be obtained when airway calibre is assessed by a method that does not entail full inspiration (see below). The sensitivity and specificity of the method have been reported [53, 54, 61].

Problem with the measurement. A bronchoconstrictor response to methacholine is not specific to persons who are atopic or have asthma. It can also occur but to a lesser extent in healthy subjects. This response is reduced if the challenge is repeated within 6 h [62]. It is apparent when monitoring is by measurement of airways conductance (PC_{35},s*G*aw) or when the forced oscillation method is used. An unambiguous result is also likely when the response is monitored using measurement of trans-cutaneous oxygen tension [53]. However, using FEV_1, the inspiration to total lung capacity initiates a bronchodilator reflex (Section 12.5.1). This can sometimes reverse the small degree of bronchoconstriction found in subjects who are not hyper-responsive. In this event the FEV_1 is unchanged and the response is negative [63]. In hyper-responsive subjects the constrictor stimulus is the stronger of the two and so FEV_1 falls, yielding a positive result [64]. Thus, the outcome of the test reflects a balance of forces and may not always be as conclusive as was thought to be at one time.

15.8.3 Exercise-induced airflow limitation

Background. Exercise can induce bronchoconstriction in persons with reactive airways and raised bronchomotor tone [54]. In such persons the cooling and drying of the airway epithelium that results from exercise can stimulate the release from mast cells of endogenous histamine, cysteinyl leukotrienes and other inflammatory mediators. A similar response can occur as a result of breathing cold air and the two effects summate. Hence, in the UK a typical initial manifestation of the condition is when the subject hurries out of the house on the first frosty morning of winter. However, in a hot dry environment, exercise leading to dehydration of the airways can cause bronchoconstriction in the absence of cooling. Thus, the two effects can occur independently.

Exercise-induced bronchoconstriction (EIB) is also called exercise-induced asthma (EIA). It is provoked by and develops shortly after a few minutes of near-maximal exercise of rapid onset. A period of warm up can provide protection and the obstruction can wear off if the exercise is prolonged [53]. A positive response is followed by a refractory period lasting up to 4 h [65]. These features need to be taken into account if a valid result is to be obtained.

Indications/contraindications. The usual application is to validate a diagnosis of EIB in a person with symptoms suggestive of the condition but who has a normal FEV_1. The test is also used to confirm the effectiveness of corticosteroid therapy. In children the test can be used to confirm a diagnosis of asthma [66] and as a method in epidemiological studies (Section 8.2.5). The contraindications include both those given in Table 15.5 and others that are specific to exercise, for example unstable cardiac arrhythmia, some arrhythmias and material hypertension (Table 29.3, page xxx).

Procedure. Susceptibility to EIB is assessed by measurement of FEV_1 6 min before and 6 min after a period of moderately heavy exercise of duration 6–8 min. The FEV_1 should fall by at least 10% and be restored by a subsequent inhalation of salbutamol. Running, cycling or stepping exercise can be used, but not swimming as that exercise provides a less powerful constrictor stimulus [67]. On this account swimming is often a suitable recreation for persons with asthma.

Practical details. The medical condition of the subject and the facilities in the exercise laboratory should conform to the normal practices for exercise testing (Chapter 29). However, in the case of children who are reasonably active there is only need for a space where they can run or jump; a laboratory is not necessary [68]. The ambient temperature and relative humidity of the air should be on the low side of normal. If practicable the respired gas should have been dried or delivered from a source of compressed air. The subject should breathe through the mouth and wear a nose clip. No prior bronchodilator therapy and preferably no drink containing caffeine should have been taken on the day of the test. The FEV_1 should be measured prior to exercise. This should be of sufficient intensity to raise the exercise ventilation and cardiac frequency, respectively, to approximately 60% and 80% of the predicted maximum (e.g. Section 28.8.3). The appropriate level of exercise should be achieved within a time of 4 min; it should be maintained for 4 min (or 6 min if the onset is abrupt as when performing shuttle running). The total duration of exercise should be 6–8 min. The spirometry is repeated 6 min after the end of exercise.

Comment. The reproducibility of the reduction in FEV_1 for tests repeated within 4 weeks is of the order of 20%. The procedure is well tolerated by children and physically active adults.

15.8.4 Cold air provocation test

This test is usually performed at rest and does not entail pharmacologically active substances. In addition, when the response is monitored by the forced oscillation (impedance) method there is no need for the subject to perform respiratory gymnastics. Hence, the procedure is particularly suitable for elderly subjects and young children [69, 70]. The provoking agent is air which is cooled to –10°C by passage through a coil surrounded by a refrigerated sheath or a bucket of ice and salt. The subject breathes the air through the mouth for up to 10 min taking deep rapid breaths and hypocapnia is avoided by using a mouthpiece with a large deadspace or by providing 2% carbon dioxide as the respired gas. Other aspects of the procedure are as for exercise induced airflow limitation including the contraindications, the end-point and the refractory period [53, 54].

Fog produced by nebulising water [71, 72], or nebulised hypertonic agents such as mannitol [73] can also be used to test for bronchial hyper-responsiveness.

15.8.5 Specific bronchial challenge testing

Introduction

Bronchial challenge testing is used to establish whether or not a person's asthma or other symptoms are caused by sensitisation to a particular substance to which he or she has been exposed [74]. The exposure usually arises at work and the information can help to secure long-term respiratory health and/or financial compensation. The procedure is not without risk so, except when the context is a medical one, the case for obtaining the information should be reviewed impartially before the test is performed. The review is likely to include the results of other tests, e.g. some of those listed in Table 15.4.

Temporal variation

This can take the form of variation either between morning and evening (*circadian variation*) or over a working shift or working week. The presence of circadian variation is evidence for non-specific bronchial hyper-responsiveness, such as can occur with asthma, but not usually with COPD (e.g. Fig. 15.6). The information is obtained by having the patient record his or her peak expiratory flow (PEF) every 4 h except during sleep.

Variation in PEF over a shift or working week. This can be used to investigate a possible occupational cause for wheeze or other symptom. The procedure is of greatest use if the occupational exposure is of low intensity, for example as a result of inadequate occupational hygiene measures or if the asthmatic response is of the delayed onset type (e.g. Fig. 37.11, page xxx). Occupational asthma of immediate onset is usually diagnosed by the patient.

Positive findings are likely to include (a) decline in PEF over a shift, (b) progressive deterioration over consecutive days at work, hence usually over the working week, (c) recovery during any period away from work, for example at week ends or after a holiday. The information is best obtained by the subject measuring the PEF every 2 h whilst at work, starting before entering the work place. However, measurements 4 times daily are nearly as good. Morning and evening measurements provide insufficient information [76]. The duration of measurements should be a minimum of 5 consecutive days, but usually the effects of breaks and a holiday should be included as well. The data points are displayed as graphs (Fig. 15.7); these are best interpreted by an experienced or trained observer or using a computer programme

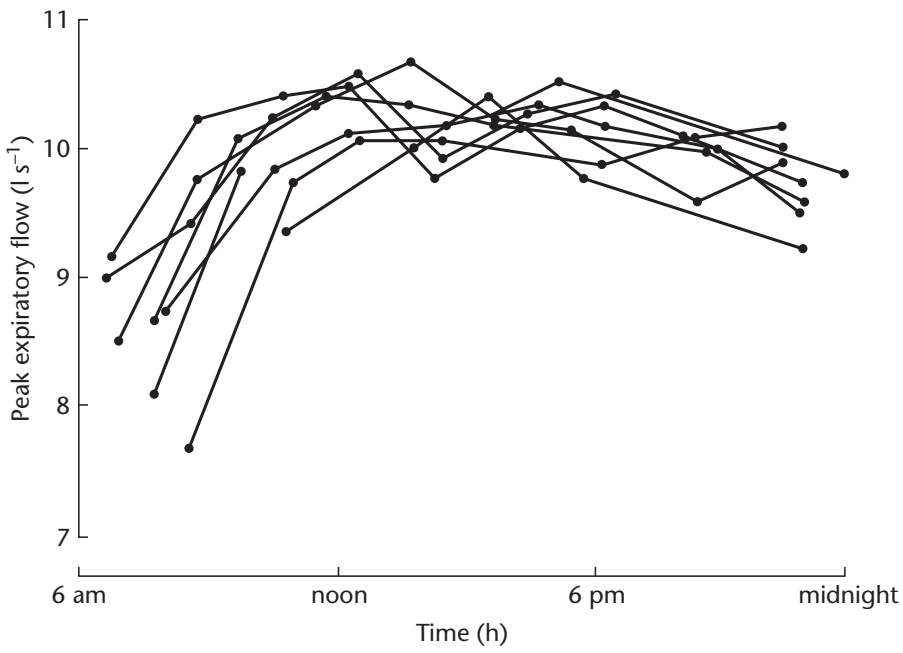

Fig. 15.6 Circadian measurements of peak expiratory flow rate in a pigeon fancier (precipitin positive) with exercise induced airflow limitation. There was a morning dip pattern which was reproducible from day to day. The morning dip was *not* reduced following 2 weeks away from pigeons; hence the airflow limitation was unlikely to have been related to that exposure. Source: [75].

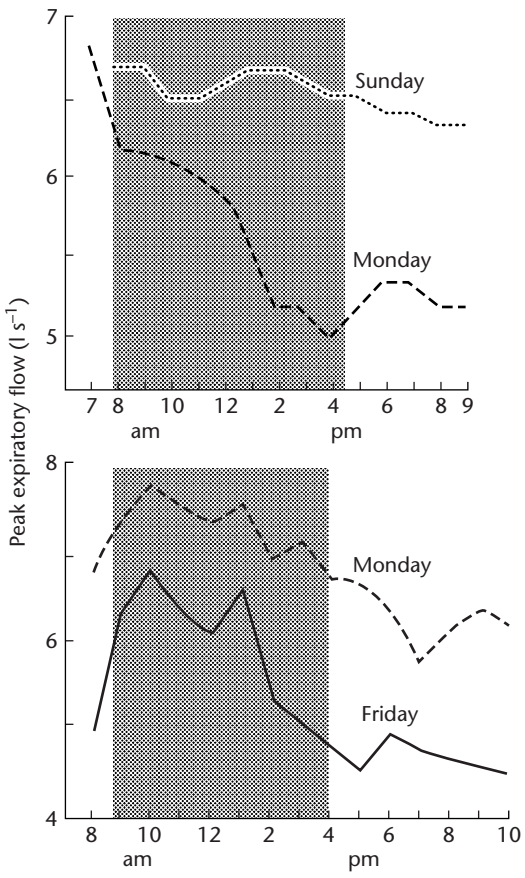

Fig. 15.7 Circadian values for peak expiratory flow in two electrical workers who became sensitised to colophony. The upper record shows progressive airways obstruction developing throughout the first working day after a rest day. The lower record shows further deterioration over subsequent days. Source: [77]

[78]. Investigators need to be alert to the possibility of subjects falsely recording their data [79] and so data logging meters are preferred for this form of testing.

Challenge with specific substances

Risks and benefits. During normal work any exposure to a specific antigen is usually mild, sensitisation builds up gradually and there is advance warning of possible future difficulties. The threat to health can be increased by failure of hygiene measures or if the exposure is unexpectedly increased by an incautious challenge, a spillage or other accident at work, or if an unfamiliar task is performed without due preparation. Any of these circumstances can threaten life.

Challenge away from the work place carries a particular risk when there is only minimal information on the susceptibility to the antigen of the person under test. Thus, challenge should be undertaken only if there is good reason for doing so. This might be (a) diagnosis or attribution in a person who is no longer exposed, (b) identification of a sensitising antigen from a mixture or (c) investigation of what appears to be a previously unidentified agent.

A positive challenge test is sometimes followed by nocturnal airway obstruction. This can be expected to respond to therapy and, in the absence of further occupational exposure, rarely lasts more than 2–3 days [74]. During this time there may be increased diurnal variation in airway calibre with a morning dip pattern. Its occurrence is further evidence for sensitisation to the substance being tested.

A person administering a challenge test is unlikely to be at risk since sensitisation appears not to develop as a result of a single exposure. However, technicians who administer the test frequently should be protected [56].

Preparations. The test is undertaken when the patient is in a stable state with no material airflow obstruction (e.g. $FEV_1 > 80\%$ predicted when off treatment) and not within a week of previous exposure to the suspected antigen or to histamine. The subject should not be taking bronchoactive drugs at the time. Challenge can be carried out either using graded doses from a dosimeter or in a manner that mimics exposure at work such as painting, welding, soldering, sifting or mixing. The manoeuvre should be performed within the hospital complex in a booth or small chamber ventilated to outside air. Full safety precautions should be available, including nebulised and intravenous bronchodilator drugs, intravenous hydrocortisone, oxygen and facilities for respiratory and cardiac resuscitation. The inhaled concentration of test substance should not exceed the hygiene standard and should be less than that experienced at work.

If the suspected allergen is soluble in water, the challenge can be undertaken using a nebulised aerosol. This should be prepared as a 10% weight-for-volume suspension in phosphate buffered saline. The suspension is agitated for 24 h at 4°C, filtered, dialysed against phosphate buffered saline, freeze-dried, resuspended at an appropriate concentration (which might be in the range 0.01–10 mg ml^{-1}) and sterilized using a multipore filter. The concentration for inhalation should initially be less than that which causes a positive intradermal reaction (Section 15.3).

Which measurements? When an immediate response to challenge is expected, this will involve the larger airways, so either the airway conductance or FEV_1 or peak expiratory flow should be monitored (e.g. Section 12.3.1). A delayed response can affect all classes of airway, or be confined to small ones. On this account the assessment should be based on a full forced expiration from which FEV_1 and flows at small lung volumes can be derived. Use of a constant pressure plethysmograph is recommended as an allowance can then be made for dynamic compression (Section 12.5.1). A late response is often accompanied by fever, leucocytosis, a fall in transfer factor and radiographic infiltrates. Thus, there is a case for monitoring some of these aspects as well.

The measurements of lung function are usually made throughout the day, initially at 5 min intervals and subsequently every hour. On day 1 the subject is instructed in the procedure and control measurements are made. On day 2, and if necessary on subsequent days, graded exposures are given and later these are repeated using a refined extract or after administration of

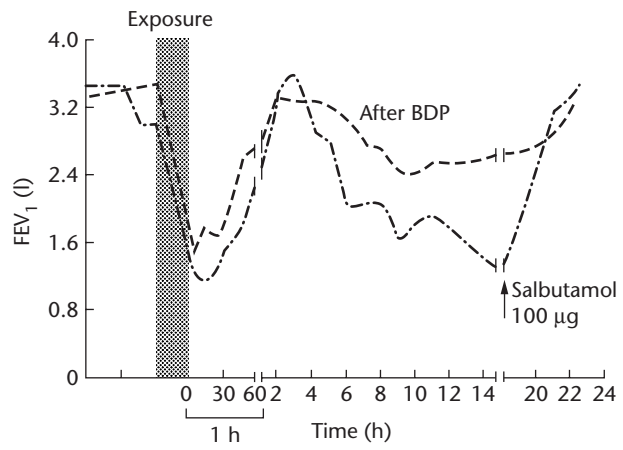

Fig. 15.8 Dual response of forced expiratory volume (FEV_1) to challenge with rye flour in a baker. The delayed but not the immediate asthmatic reaction was largely prevented by pre-treatment with beclomethasone diproprionate (BDP) but not by placebo treatment (not shown). Source: [80]

inhaled corticosteroid or other protective agent. Thus, in a study of the effects of colophony (pine resin) [77] Burge, Pepys and colleagues initially had their subjects inhale one natural breath of soldering fume, followed by three and six breaths at 15 min intervals if no reaction had occurred by then. On four subsequent days if no reaction had occurred the subjects breathed fumes on three occasions for 1 and 2 min, 5 min, 20 min and 60 min, with the subject reapplying the heated iron to the solder every 30 s throughout the exposure. In the case of an uncomplicated immediate response the measurements can be discontinued or made infrequently once the flow rate has returned to the initial value. If a delayed response is suspected the measurements should be continued into the following day. The results of the challenge tests are analysed graphically (Fig. 15.8) or used to construct a dose–response relationship; an immediate response is related to the logarithm of the dose but a late response may not be quantifiable and in this circumstance can be reported as present or absent. It can also be expressed in terms of a summary measurement, for example the mean peak expiratory flow for the 12 h following challenge or the average under the flow–time curve.

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